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(54) Title: NOVEL GENES, COMPOSITIONS, KITS, AND METHODS FOR IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF CERVICAL CANCER

(57) Abstract: The invention relates to compositions, kits, and methods for detecting, characterizing, preventing, and treating human cervical cancers. A variety of novel markers are provided, wherein changes in the levels of expression of one or more of the markers is correlated with the presence of cervical cancer.

Claims

1. An isolated nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleotide sequence which is at least 90% homologous to a nucleotide sequence of Tables 1-4, or a complement thereof;

b) a nucleic acid molecule comprising a fragment of a nucleic acid comprising the nucleotide sequence of Tables 1-4, or a complement thereof; and

c) a nucleic acid molecule comprising the nucleotide sequence of Tables 1-4, or a complement thereof.

2. A vector which contains the nucleic acid molecule of claim 1.

3. A host cell which contains the nucleic acid molecule of claim 1.

4. An isolated polypeptide which is encoded by a nucleic acid molecule comprising a nucleotide sequence which is at least 90% homologous to a nucleic acid comprising a nucleotide sequence of Tables 1-4.

5. An antibody which selectively binds to a polypeptide of claim 4.

6. A method for producing a polypeptide comprising culturing the host cell of claim 3 under conditions in which the nucleic acid molecule is expressed.

7. A method for detecting the presence of a polypeptide of claim 4 in a sample comprising:

a) contacting the sample with a compound which selectively binds to the polypeptide; and

b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a polypeptide of claim 4 in the sample.

8. A kit comprising a compound which selectively binds to the polypeptide of claim 4.

9. A method for detecting the presence of a nucleic acid molecule of claim 1 in a sample comprising:

a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and

b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a nucleic acid molecule of claim 1 in the sample.

10. The method of claim 9, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

11. The method of claim 9, wherein the sample is isolated from cervical tissue.

12. The method of claim 9, wherein the sample is a tumor sample.

13. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1.

14. A method of assessing whether a patient is afflicted with cervical cancer or has a pre-malignant condition, the method comprising comparing:

a) the level of expression of a marker in a patient sample, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4, and

b) the normal level of expression of the marker in a control non-cervical cancer sample,

wherein a significant difference between the level of expression of the marker in the patient sample and the normal level is an indication that the patient is afflicted with cervical cancer or has a pre-malignant condition.

15. The method of claim 14, wherein the patient has CIN.

16. The method of claim 14, wherein the patient has SIL.

17. The method of claim 14, wherein the marker corresponds to a secreted protein.

18. The method of claim 14, wherein the marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.

19. The method of claim 14, wherein the sample comprises cells obtained from the patient.

20. The method of claim 19, wherein the sample is a cervical smear.

21. The method of claim 19, wherein the cells are in a fluid selected from the group consisting of a fluid collected by peritoneal rinsing, a fluid collected by uterine rinsing, a uterine fluid, a uterine exudate, a pleural fluid, a cystic fluid, and an cervical exudate.

22. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a protein corresponding to the marker.

23. The method of claim 17, wherein the presence of the protein is detected using a reagent which specifically binds with the protein.

24. The method of claim 23, wherein the reagent is selected from the group consisting of an antibody, an antibody derivative, and an antibody fragment.

25. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a transcribed polynucleotide or portion thereof, wherein the transcribed polynucleotide comprises the marker.

26. The method of claim 25, wherein the transcribed polynucleotide is an mRNA.

27. The method of claim 25, wherein the transcribed polynucleotide is a cDNA.

28. The method of claim 25, wherein the step of detecting further comprises amplifying the transcribed polynucleotide.

29. The method of claim 14, wherein the level of expression of the marker in the sample is assessed by detecting the presence in the sample of a transcribed polynucleotide which anneals with the marker or anneals with a portion of a polynucleotide wherein the polynucleotide comprises the marker, under stringent hybridization conditions.

30. The method of claim 14, wherein the level of expression of the marker in the sample differs from the normal level of expression of the marker in a patient not afflicted with cervical cancer by a factor of at least about 2.

31. The method of claim 14, wherein the level of expression of the marker in the sample differs from the normal level of expression of the marker in a patient not afflicted with cervical cancer by a factor of at least about 5.

32. The method of claim 14, comprising comparing:

a) the level of expression in the sample of each of a plurality of markers independently selected from the markers listed in Tables 1-4, and

b) the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with cervical cancer,

wherein the level of expression of more than one of the markers is significantly altered, relative to the corresponding normal levels of expression of the markers, is an indication that the patient is afflicted with cervical cancer or a pre-malignant condition.

33. The method of claim 32, wherein the level of expression of each of the markers is significantly altered, relative to the corresponding normal levels of expression of the markers, is an indication that the patient is afflicted with cervical cancer.

34. The method of claim 32, wherein the plurality comprises at least three of the markers.

35. The method of claim 32, wherein the plurality comprises at least five of the markers.

36. A method for monitoring the progression of cervical cancer or a pre-malignant condition in a patient, the method comprising:

a) detecting in a patient sample at a first point in time, the expression of a marker, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4;

b) repeating step a) at a subsequent point in time; and

c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of cervical cancer or a pre-malignant condition in the patient.

37. The method of claim 36, wherein the marker corresponds to a secreted protein.

38. The method of claim 36, wherein marker corresponds to a transcribed polynucleotide or portion thereof, wherein the polynucleotide comprises the marker.

39. The method of claim 36, wherein the sample comprises cells obtained from the patient.

40. The method of claim 39, wherein the patient sample is a cervical smear.

41. The method of claim 39, wherein between the first point in time and the subsequent point in time, the patient has undergone surgery to remove a tumor.

42. A method of assessing the efficacy of a test compound for inhibiting cervical cancer in a patient, the method comprising comparing:

a) expression of a marker in a first sample obtained from the patient and exposed to the test compound, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4, and

b) expression of the marker in a second sample obtained from the patient, wherein the sample is not exposed to the test compound,

wherein a significantly lower level of expression of the marker in the first sample, relative to the second sample, is an indication that the test compound is efficacious for inhibiting cervical cancer in the patient.

43. The method of claim 42, wherein the first and second samples are portions of a single sample obtained from the patient.

44. The method of claim 42, wherein the first and second samples are portions of pooled samples obtained from the patient.

45. A method of assessing the efficacy of a therapy for inhibiting cervical cancer in a patient, the method comprising comparing:

a) expression of a marker in the first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4, and

b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy,

wherein a significantly lower level of expression of the marker in the second sample, relative to the first sample, is an indication that the therapy is efficacious for inhibiting cervical cancer in the patient.

46. A method of selecting a composition for inhibiting cervical cancer in a patient, the method comprising:

a) obtaining a sample comprising cancer cells from the patient;

b) separately exposing aliquots of the sample in the presence of a plurality of test compositions;

c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4; and

d) selecting one of the test compositions which induces a lower level of expression of the marker in the aliquot containing that test composition, relative to other test compositions.

47. A method of inhibiting cervical cancer in a patient, the method comprising:

a) obtaining a sample comprising cancer cells from the patient;

b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;

c) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4; and

d) administering to the patient at least one of the test compositions which induces a lower level of expression of the marker in the aliquot containing that test composition, relative to other test compositions.

48. A kit for assessing whether a patient is afflicted with cervical cancer or a pre-malignant condition, the kit comprising reagents for assessing expression of a marker selected from the group consisting of the markers listed in Tables 1-4.

49. A kit for assessing the presence of cervical cancer cells or pre-malignant cervical cells or lesions, the kit comprising a nucleic acid probe wherein the probe specifically binds with a transcribed polynucleotide corresponding to a marker selected from the group consisting of the markers listed in Tables 1-4.

50. A kit for assessing the suitability of each of a plurality of compounds for inhibiting cervical cancer in a patient, the kit comprising:

a) the plurality of compounds; and

b) a reagent for assessing expression of a marker selected from the group consisting of the markers listed in Tables 1-4.

51. A method of making an isolated hybridoma which produces an antibody useful for assessing whether a patient is afflicted with cervical cancer or a pre-malignant condition, the method comprising:

isolating a protein or protein fragment corresponding to a marker selected from the group consisting of the markers listed in Tables 1-4;

immunizing a mammal using the isolated protein or protein fragment;

isolating splenocytes from the immunized mammal;

fusing the isolated splenocytes with an immortalized cell line to form hybridomas; and

screening individual hybridomas for production of an antibody which specifically binds with the protein or protein fragment to isolate the hybridoma.

52. An antibody produced by a hybridoma made by the method of claim 51.

53. A kit for assessing the presence of human cervical cancer cells or pre-malignant cervical cells or lesions, the kit comprising an antibody, wherein the antibody specifically binds with a protein corresponding to a marker selected from the group consisting of the markers listed in Tables 1-4.

54. A method of assessing the cervical cell carcinogenic potential of a test compound, the method comprising:

a) maintaining separate aliquots of cervical cells in the presence and absence of the test compound; and

b) comparing expression of a marker in each of the aliquots, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4,

wherein a significantly enhanced level of expression of the marker in the aliquot maintained in the presence of the test compound, relative to the aliquot maintained in the absence of the test compound, is an indication that the test compound possesses human cervical cell carcinogenic potential.

55. A kit for assessing the cervical cell carcinogenic potential of a test compound, the kit comprising cervical cells and a reagent for assessing expression of a marker, wherein the marker is selected from the group consisting of the markers listed in Tables 1-4.

56. A method of treating a patient afflicted with cervical cancer, the method comprising providing to the patient an antisense oligonucleotide complementary to a polynucleotide corresponding to a marker selected from the markers listed in Tables 1-4.

57. A method of inhibiting cervical cancer in a patient at risk for developing cervical cancer, the method comprising inhibiting expression of a gene corresponding to a marker selected from the markers listed in Tables 1-4.

Table 1

CCAGATTACACATCCCCAGTGGTGCTTCCTTACTTCGAGCGGGCCGCCCCGGGCAGGGTA
CTTCACACCAAACACTAGCTCAAGCACTGACGTTATTCTACAGGACTATGAACCTTCATA
TCCACATTTACAGTCCGGACAGATAAAGGAAAACAACCCAAATCCAGGAGGCAATATAAA
AGGAAGAGAACAAAACACACATTCATACACTCACACTTAAAAATAGGGGAAGACCAACAG
GGGAACTTTTCGTTCTCTTCCTGGGATGTCTACTTAAAAATCCCATGTGGGTACCT
Sequence 554
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G
AATCAGTTCAGTGTAGACATTTTGAAAAGATTGTTTCCTGTGCTCTACGATAGCTTAGT
G
CAATGTGCACTTCTGTTTTACTTGCCATTTTCCTGCTCTGTTTTCTCTGTGACATGAAG
C
AACAGAAACTGAGATCAAAGTTAAGATTATATCCTGTTTGTAGTATCAGATATTTTTCT
G
TGTACATTTACATTCAAGTTTGATAACACTGGTGGTTTCATTTCAATACAAATTATGCTA
GAGAACTGACATTTTCANACATGGTCATATATATGCTATTTGAATTCCTTTATCTTGATA
CCAGATCTTGGATTGTGAATCTCTTGATGATAGATGTGCAGCTAATTTTGTCCCGAAA
CT

Sequence 555
GGGTGGCGGCCGCCCGGGCAGGTACAAGACCATGACACCGCCCAAAACACTTCCTGCAGA
TGTTGTCGTTGGAAAACTGTCGTCTTACAGAAGCCAGTTGCAAGGACCTTGCTGCTGTCT
TGGTTGTCAGCAAGAAGCTGACACACCTGTGCTTGGCCAAGAACCCCCATTGGGGGATAC
AGGGGTGAAGTTTCTGTGTGAGGGCTTGAGTTACCCTGATTGTAAACTGCAGACCTTGGT
GTTACAGCAATGCAGCATAACCAAGCTTGGCTGTAGATATCTCTCAGAGGCGCTCCAAGA
AGCCTGCAGCCTCACAAACCTGGACTTGAGTATCAACCAGATAGCTCGTGGGATTGGTGG
GATTCTCTGTCAGGGCATTAGAGAATCCAAACTGTAACCTAAAACACCTACGGTTGAAGA
CCTATGAAACTAATTTTGGAAATCAAGAAACTTTTTGANNGNAAGTGAAAGGAAAA
Sequence 556
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T
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CTGGGCTTCAGAGGAGCCAGCCGCCTCCGAGTTGTCTTGGAAGTGAGGCTCTGCTGTAGT
CCTGTTCTTCTGGCTCTAAGATCTGAATGTTGTGACCACTAATTTGCTNTTTCCTGGA
GG
GTAACCCCAGTTTGGTCCACAAGGGCTT
G
Sequence 557
GAGCCCGCGGTGGCGGCCGAGGTACTGGATGTCAGGTCTGCGAAACTTCTTAGATTTTGA
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TGGAGTGAAAACTTCGGTTGCTGGCAGGTCCGTGGGAAAATCAGTGACCAGTTCATCAGA
TTCATCAGAATGGTGAGACTCATCAGACTGGTGAGAATCATCAGTGTCATCTACATTCGA
GCGGCCGCCCGGGCAGGTACCGCGGGGGGAGCGGGCCCTACCGTGTGCGCAGAAAGAGGA
GGCGCTTGCCTTCAGCTTGTGGGAAATCCCGAAGATGGCCAAAGACAACTCAACTGGTTC
GTTGCTTTCCAGGGCCTGCTGATTTTTGGAAATGTGATTATT
Sequence 558
CCGCGGTGGCGGCCGAGGTACTTTTTTTTTTTTTTTTTTTTTTTGTTTTTGAGACGGAG

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Table 1

GTCACTGG
Sequence 700
CGGCCGACTTGATGAGCGGAGAGACCTGCACCGGTGGCACCATCTTGTCCCTGACCTCCG
CACCGGAAGCCCCCGCGTACCT
Sequence 701
ACCGCGGTGGCGGCCGAGGTACGCGGGGGAGAGAGGAAAAGAACACAGATCTCGCATGGT
TCAGATTTTTCTTTTTAGGTCCAGGAGTAAGATATATCATACGAAAATGAAAATTATAAT
NCTTCTTGGATTCCTGGGAGCCACATTGTCAGCCCCACTTATCCCACAGCGTCTCATGTC
TGCAGCAATAGCAATGAGTTACTTCTTAATCTTAATAATGGTCAACTTTTGCCACTACAA
CTTCAGGGCCCACTTAATTCATGGATTCCACCTTTCTCTGGAATTTTACAACAGCAGCAG
CAGGCTCAAATTCCAGGACTCTCCCAGTTCTCTTTATCAGCTCTAGACCAGTTTGCTGGA
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AGGCCAAGGTTGATCCCTTACAGCTTCAAACACCGGCTTNAAACACAACCAGGCCCCAGT
CACGGGGATGCCCTATGTATTCTCCTTCAAAATGCCTTAAGAGCAAGGGCCAGATGGTTT
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CCGCGGTGGCGGCCGCCCGGGCAGGTACTGCAAGCAACAGTTACTGCGACGTGAGATCAT
CAAGAACACGTAGAGAAACCCAGCTGTAATCATGCATGGAGATACACCTACATTGCATGA
ATATATGTTAGATTTGCAACCAGAGACAACTGATCTCTACTGTTATGAGCAATTAAATGA
CAGCTCANAGGAGGAGGATGAAATAGATGGTCCAGCTGGACAAGCAGAACCGGACAGAGC
CCATTACAATATTGTAACCTTTTGTTGCAAGTGTGACTCTACGCTTCGGTTGTGCGTACC
T
Sequence 702
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CACAGACGGGGTGGTTCTAGACGGCCGCTCTAGAACTNGTGGGATC
Sequence 703
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GTTGTCAGCAAGAAGCTGACACACCTGTGCTTGGCCAAAGAACCCATTTGGGGATACANG
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TACAGCAATGCAGCATAACCAAGCTTGGCTGTAGATATCTCTCAGAGGCGCTCCAAGAAG
CCTGCAGCCTCACAAACCTGGACTTGAGTATCAACCAGATAGCTCGTGGGATTGGTGGGA
TTCTCTGTCAGGCATTAAGAAGAATCCAAACTGTAACCTAAAACACCTACGGTNTGAAGA
CCTATGAAACTAATTTGGGAAATCAAGAAGCTGTTGGAGGGAAAGTGA
Sequence 704
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ANGATATCCCTTCAGCCTGAGGGAATTGATGTTGATGAACCCGGAGGCATCAGTTGGCTC
ATAATCACCCTGCACGTTCATGCTCACCAGCTCCTNATTGTNNAGAGACAGNCNGGGACT
CCCGGCCGAGGATGTACCT
Sequence 705
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Sequence 706
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TTTCTTAGATAACCATAAAACTGCAAAAGCAATTTTTAAAAATGTAAATAGGACTTCATC
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CCTATATCCACTAGTATGGCTATAATAAAAAAGAGTAACAAACCGTTGAGGAGGATATGG
AGAAACTCGAGCCCTGGTCAGGTGTGGTGGATCACACCTGTAATTTCAACACTTTGGGA
Sequence 707
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GCCCCTGCTACTTACACAGTCCAGAATCACTTGGGTGAGCATTCCAGTAGGACGGTGGCA
TTTTAGGATTCAGAATATTAACCTATAAACCTGTCATTTGATTCTTGATTATTAATGTCT

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